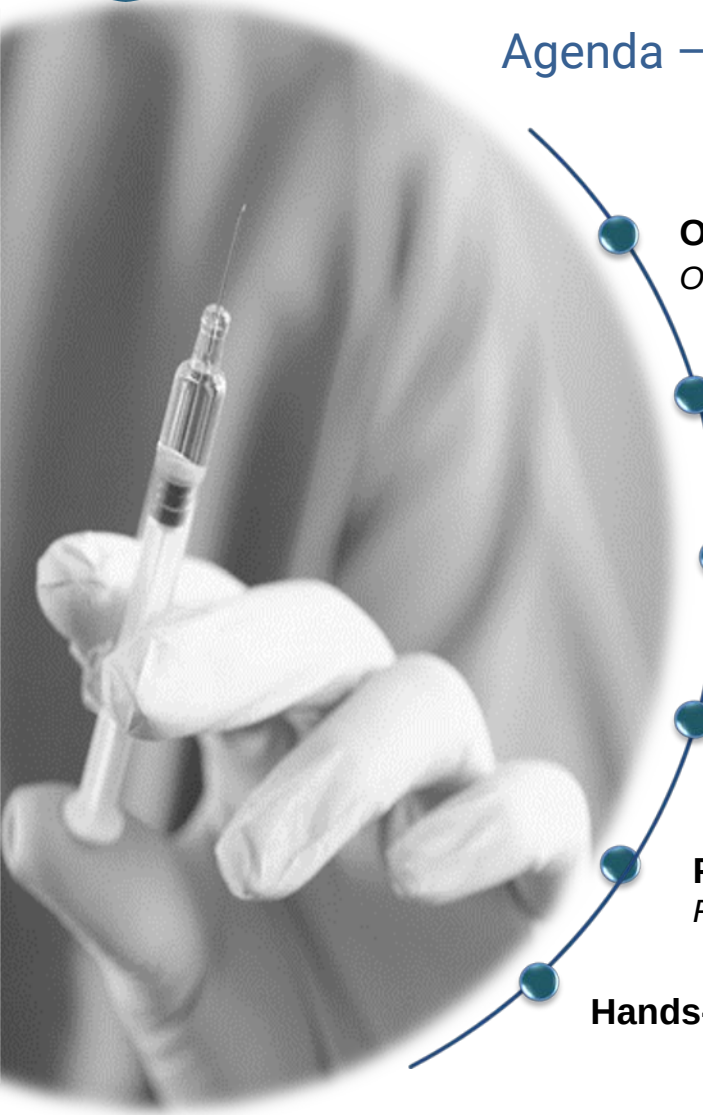
Agenda – DAY 1



Overview and Introduction into Pre-filled Syringe Market
Overview & Trends • Stakeholders • User's perspective

Technical Aspects
Syringe • Plunger • Needle • Needle shield or Tip cap • Autoinjector • Regulatory guidelines and technical standards

Overview & Introduction into Drug-Syringe Interactions
Aggregation • Degeneration • Oxidation • Viscosity • Bubbles

Overview & Introduction to manufacturing Process of PFS
Syringes Barrel Forming • Washing • Siliconization • Sterilization • Regulatory guidelines and technical standards …

Fill and Finish
Filling • Stoppering • Assembly • Technical Standards

Hands-on Session 1

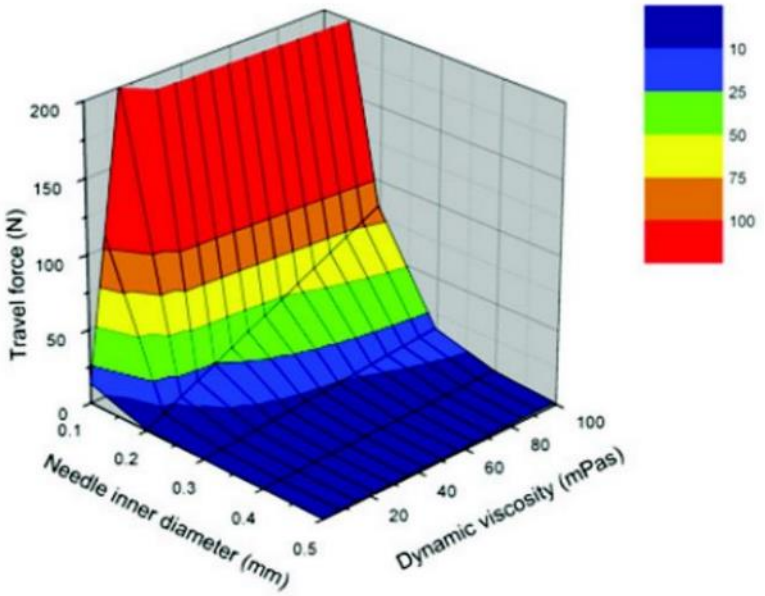
Drug features

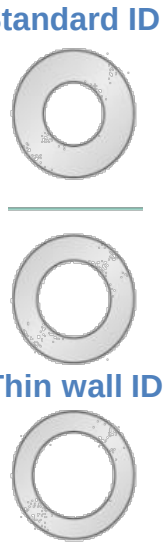
- Viscosity, pH, concentration
- Volume
- Sensitivity
  - Light
  - Oxygen
  - Temperature
  - Particles
  - Silicone oil
  - Storage
  - Vibration
  - Shear forces
  - Rubber components
  - Tungsten, glue, steel

Drug-syringe Interactions

Viscosity

- Viscosity defines syringe expression force
- Needle inner diameter and length determine force





Calculated travel force as a function of needle inner diameter and dynamic viscosity for an injection rate of 0.1 mL/s using a syringe with an inner diameter of 4.6 mm and a needle of 20 mm length applying the Hagen-Poiseuille equation

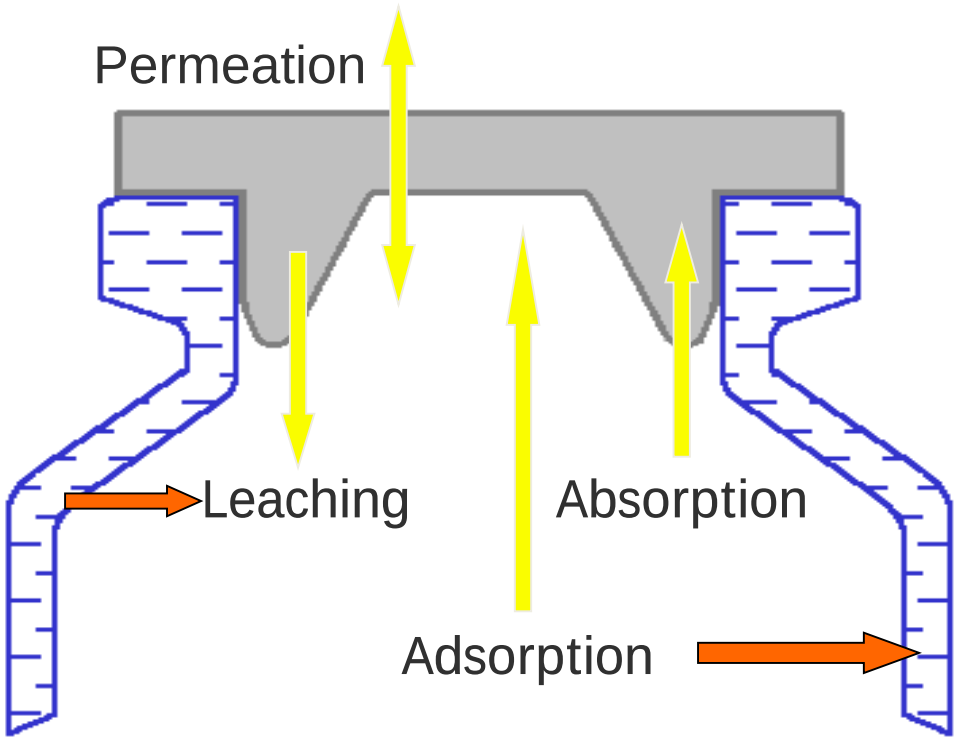
from
Adler, Michael: Challenges in the Development of Pre-filled Syringes for Biologics from a Formulation Scientist's Point of View. American Pharmaceutical Review, Feb. 2012

$$F = 8\,Q\,\mu\,L/\pi R^4 \,{}^*A$$

Hagen-Poiseuille equation

F= Frictionless travel force
L = Needle length
Q = Volumetric flow rate
R = Needle inner diameter
μ = Fluid viscosity
A = Cross sectional area of syringe plunger

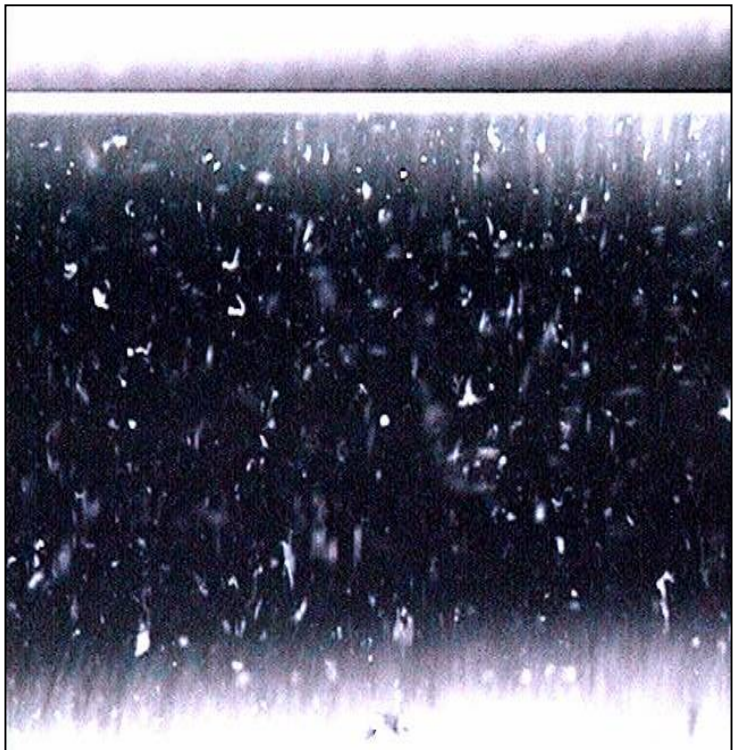
Possible Interaction of Drug Product and Elastomeric Closures



These four interactions generally occur at a low rate

Observed Interactions of Proteins with Pharmaceutical Elastomers

- Dimerization
- Aggregation (e.g. due to free subvisible silicone oil)
- Adsorption of API (at elastomers and container walls)
- Increased immunogenicity (interactions with leachables)
- OOS results for moisture content (e.g. for lyophilized products)



Silicone aggregation in a glass syringe (protein drug)

Definitions

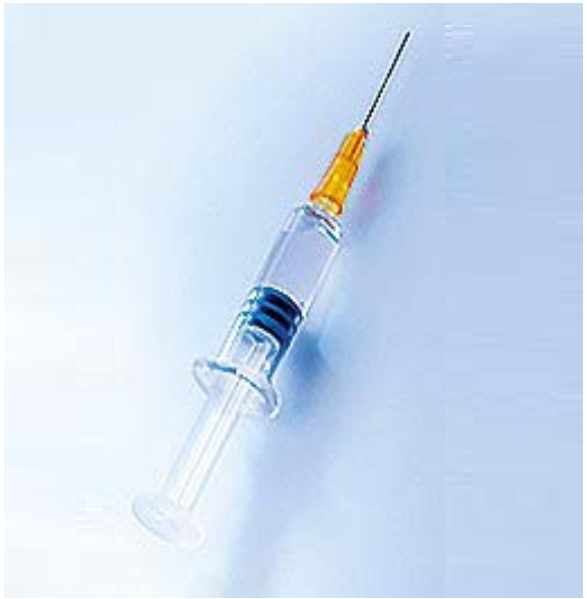
Extractable

Compounds forced/extracted from a container closure component/system in the presence of an appropriate solvent

Leachable

Compounds that leach from elastomeric, plastic components or coatings of the container and closure system as a result of direct contact with the drug formulation

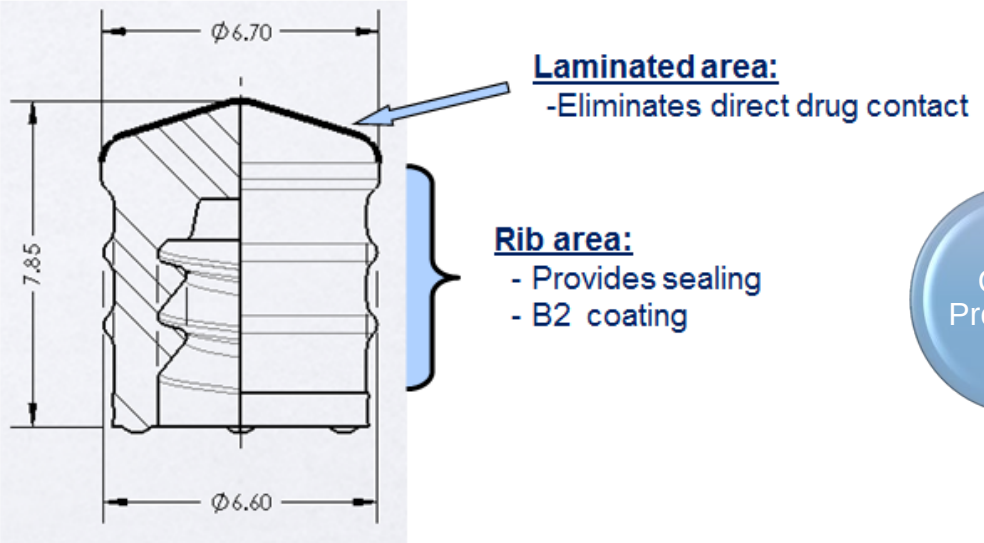
not all Extractables are Leachables

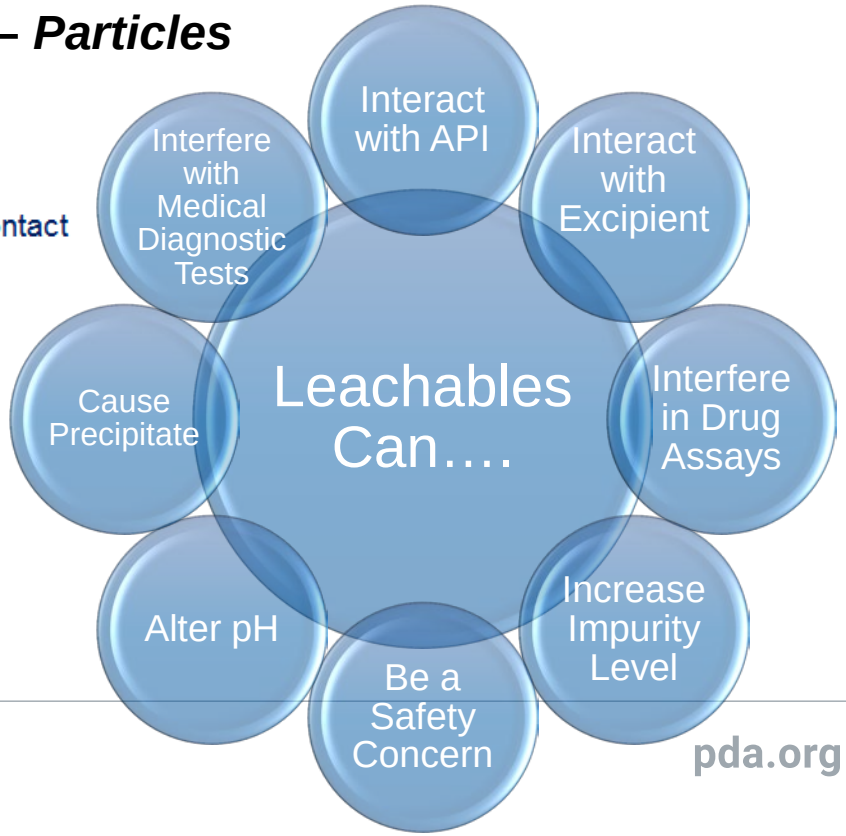


Minimizing Drug Safety Risk

Lamination fluorpolymer barrier film Advantages

- Barrier against organic and inorganic compounds **– *Extractables***
- Minimizes interaction between drug/closure **– *Leachables***
- Reduces adsorption and absorption of drug product **– *Potency***
- Eliminates need for adding silicone oil **– *Particles***



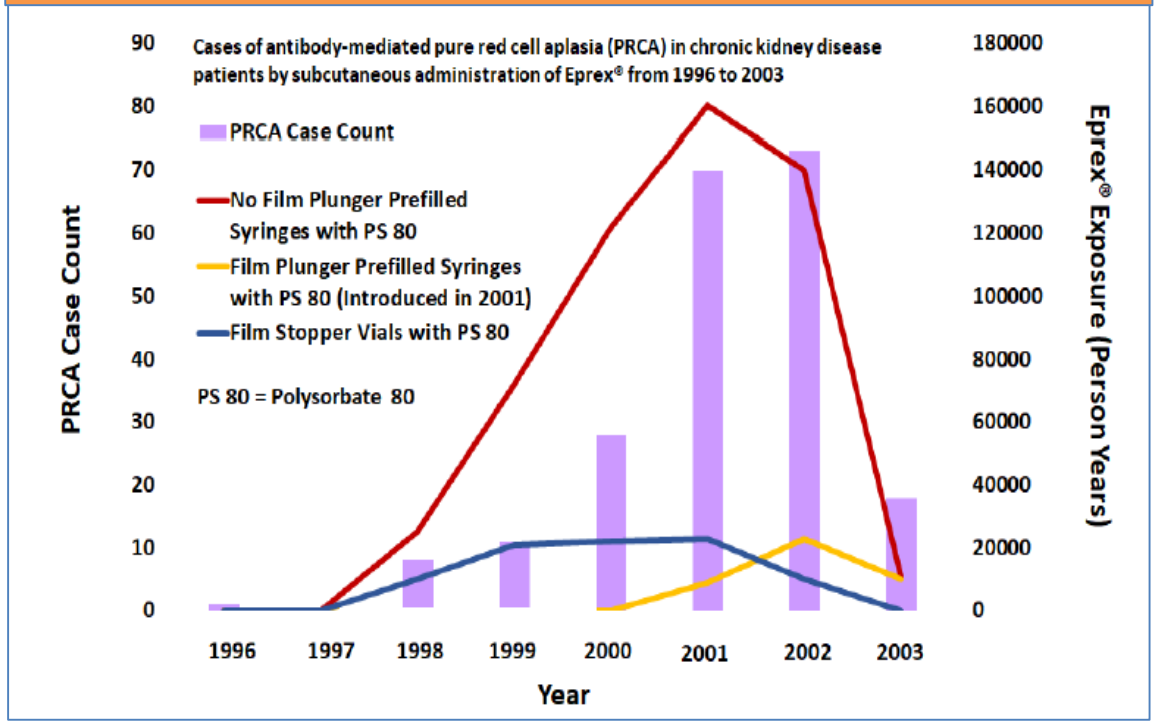


FluroTec® Products Protecting Drug Product Quality and Safety

- FluroTec film has been shown to reduce leachables based on both clinical use as well as empirical data, demonstrating reduction of gas permeation into vial headspace and minimal to no migration into liquid when challenged with strong solvents and harsh conditions.

- A Clinical example demonstrating protective barrier properties:
  - Eprex® packaged using FluroTec laminated stoppers reduced the incidence of pure red cell aplasia (PRCA) by creating a barrier to a rubber accelerator leaching from the elastomer.

Incidence of PRCA before and after FluroTec[4] film



Eprex® is a registered trademark of Johnson & Johnson

4 Boven, K, et.al., The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes, Kidney Int. 2005 Jun;67(6):2346-53.

Drug-syringe Interactions I

Bubbles

- Generated in filling process
- Less bubbles in vacuum stoppering
- Bigger bubble in vent tube stoppering

- Transport test recommended
- Moving bubble during transport
- Potential effect on drug formulation

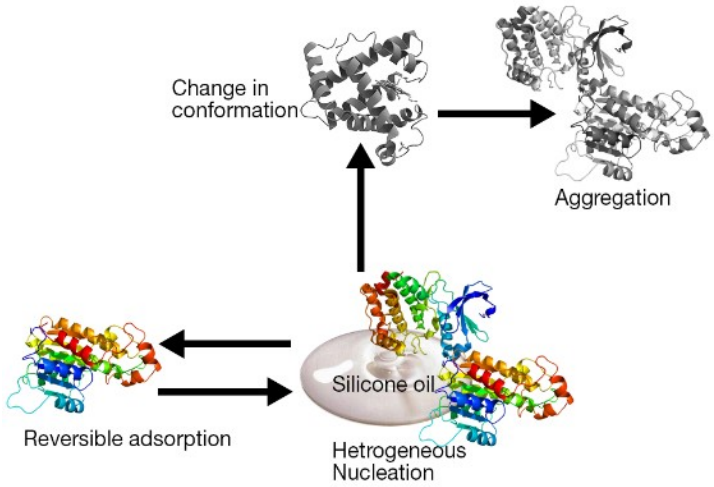
- Expansion and plunger movement risk in air transport (CCI harmed)
- Air means oxygen

Drug-syringe Interactions II

Various interactions possible
- Aggregation
- Degeneration
- Oxidation
- Adsorption

You see
- Precipitation
- Blurring
- Nothing

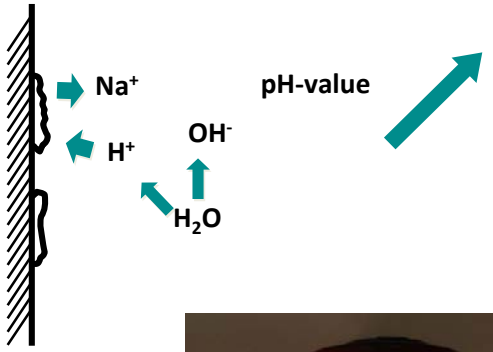
Triggered by
- Drug formulation itself
- Temperature changes, light, oxygen
- Bubbles and mechanical stress
- Barrel: silicone oil, tungsten, glue, steel
- Elastomer components: cap, stopper



What can be done?
- Stability testing
- Low tungsten, low silicone oil components
- Extractables profile of rubber components
- Reformulate or stay in vial

Drug-syringe Interactions III

Not seen in syringes – yet another benefit over vials
- pH shift
- Delamination



Why in vials, but not in syringes?
- Vial forming more stressing to glass
- Syringe inside covered by silicone oil
- More aggressive buffers and formulations filled in vials (?)
- Higher pH in vials than in PFS (?)
- PFS normally based on physiologic sodium chlorine solution (?)

Options
- Surface treatment of vials (SiO_2, Ammonium sulphate)
- Special high resistance glass vials
- COP vials
- Reformulate